The FDA Perspective on Thrombogenicity Testing of Coronary Interventional Devices:

Insights From the Large Animal Testing

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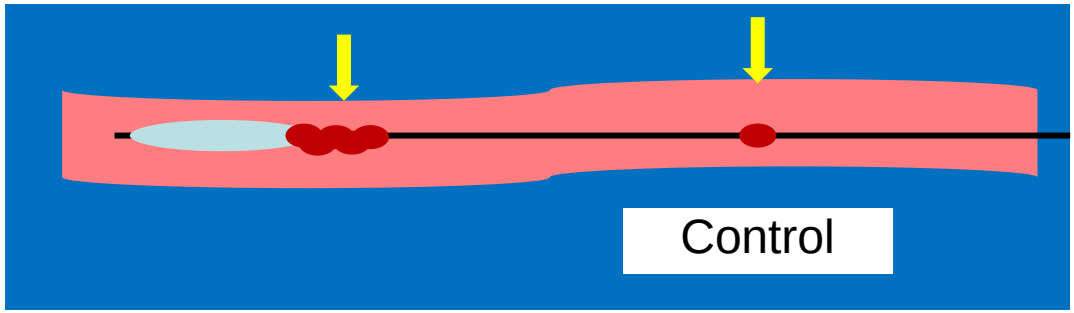
Outline

- Thrombogenicity Testing in the Canine Model
- Thrombosis Evaluation in Large Animal Testing
- Animal Models
- Study Design
- Case Study
- Clinical Relevance of the Canine Thrombo Model

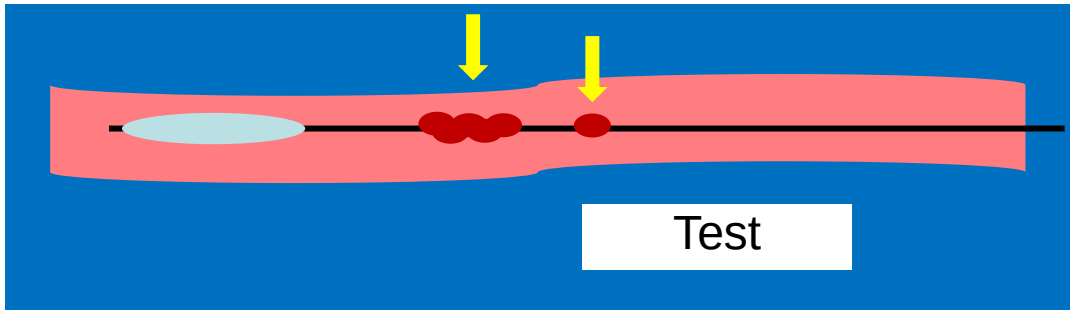
Focus on Coronary Interventional Devices

Case Study – 4 hr Jugular Canine Data

0= No thrombus present
1= Minimal thrombus
2= Moderate
3= Severe
4= Extensive,
~75% of material length



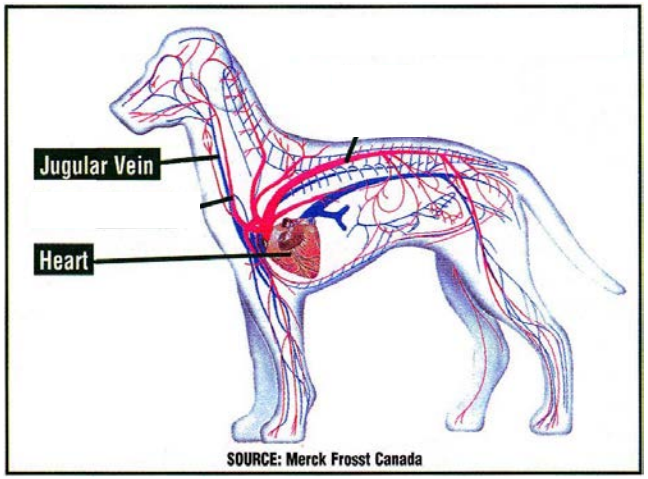
- Grade 3 thrombus formation in both groups



- What does the large animal data show?

Canine Thrombogenicity Model

- Beagle or Mongrel Dogs
- Evaluation in the Jugular Vein
- 4 hour dwell time
- Non-heparinized animals



Challenges With the In vivo Canine Thrombogenicity Model

- Survey results indicate little confidence in the reliability of this model
- Thrombogenicity is already assessed during the large animal safety studies additional in vivo canine study may not be indicated
- The Three Rs – “Refine, Reduce Replace”
  - **Replacement** refers to the preferred use of non-animal methods over animal methods whenever it is possible to achieve the same scientific aim.
  - **Reduction** refers to methods that enable researchers to obtain comparable levels of information from fewer animals, or to obtain more information from the same number of animals.
  - **Refinement** refers to methods that alleviate or minimize potential pain, suffering or distress, and enhance animal welfare for the animals used.

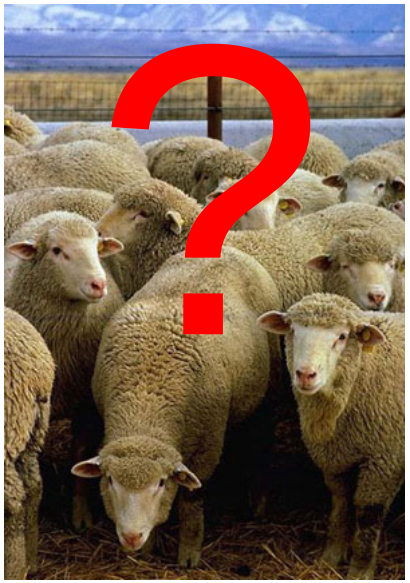
Is this analysis clinically relevant?

Rationale for Animal Testing

- Primary goal of animal testing is to demonstrate safety with some expectation of effectiveness prior to clinical testing
- Characterize deployment/implantation characteristics and failure modes
- Provide FDA with an initial assessment of how the device interacts with the biological system

Selection of Large Animal Model

- Two most widely used models are pigs and sheep
- The juvenile domestic swine and the adult Yucatan miniature swine are generally accepted models because of similarity in biologic response to humans.
  - Yucatan or Sinclair adults are better for chronic evaluation because they tend not to outgrow their stents.



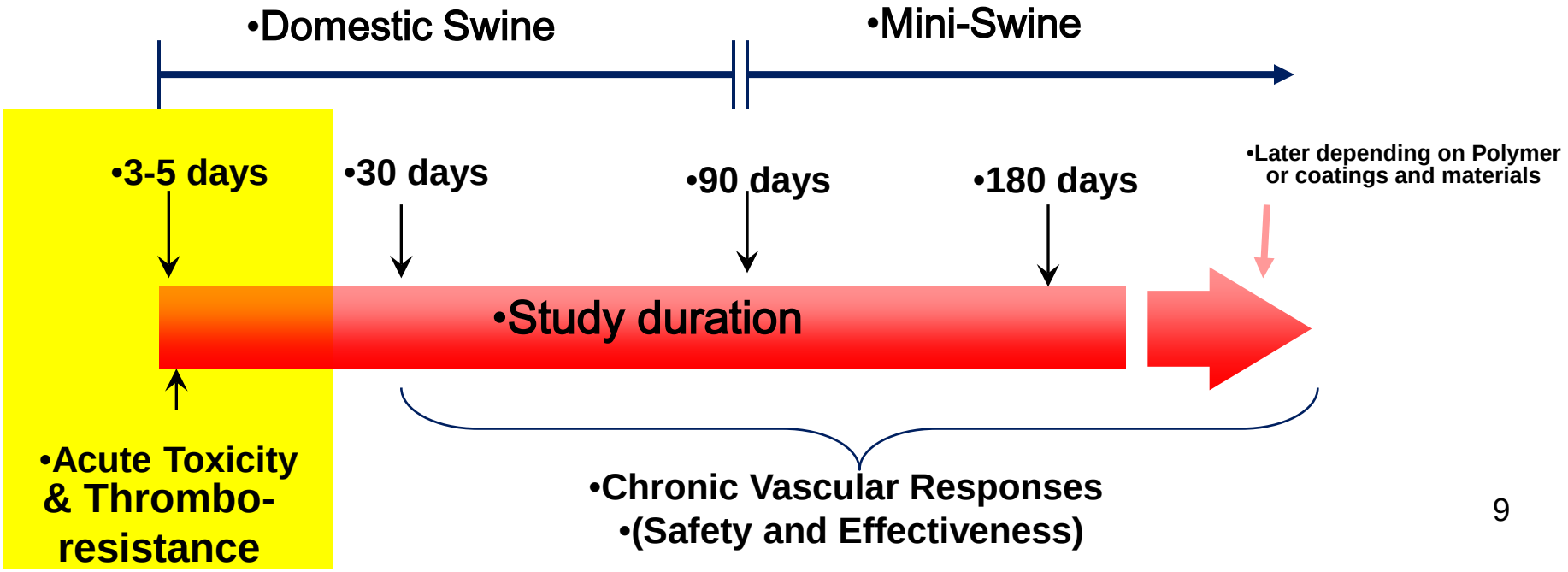
Sheep Models

- FDA is aware of the difficulties achieving appropriate anticoagulation in this model
  - Recommend cage-side ACT measurements and careful monitoring of dual anti-platelet therapy
  - Important to include descriptive narratives from the pathologist or veterinary pathologist describing all thrombotic events such that FDA can understand whether these were species-specific or device-related events.
  - Suitable for thrombogenicity testing as well

Overview of DES Study Design

- n=6-8 samples/group
- Acute and Chronic timepoints
- Control BMS (DES optional)
- Overlap and Max Dose Testing
- Bioabsorbable Stents – evaluation of materials until completely degraded

•Late chronic study timepoints should be chosen based on PK data (elution kinetics & degradation profile)



Acute vs Late Stent Thrombosis:

Not the same process

Acute Thrombosis

- *Soon after device implantation*
- *Stent and catheter*
- *Material properties*
- *Device design*

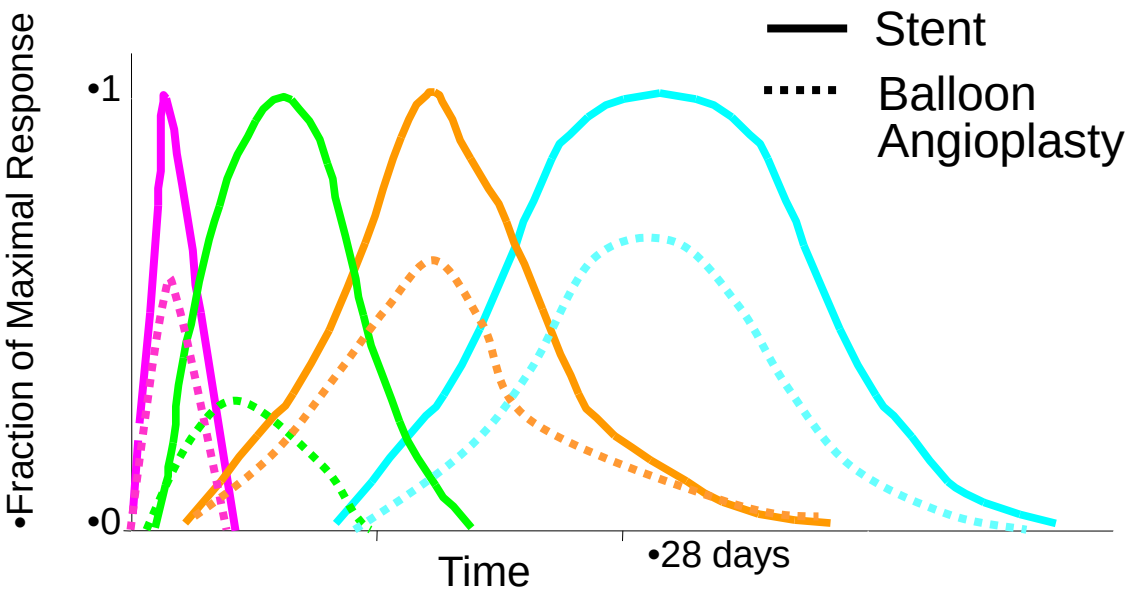
Late Thrombosis

- Long-term reaction
- Stent only
- Additional factors: Endothelial recovery (strut coverage) Inflammation

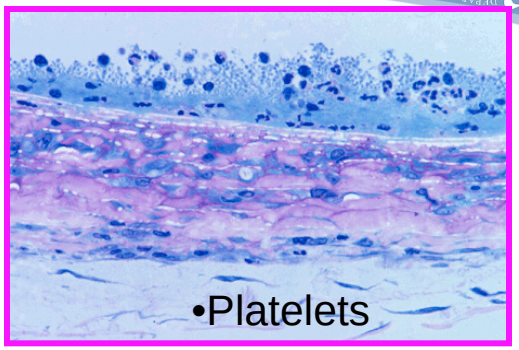
In Vivo Canine Model

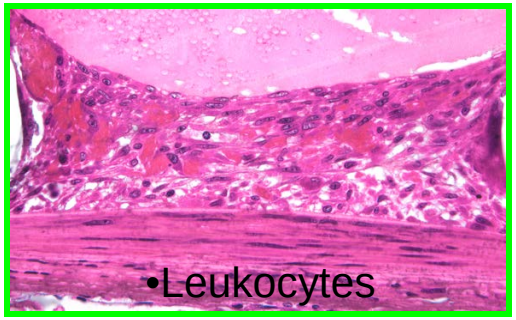
In Vivo Large Animal Model (Swine and Ovine)

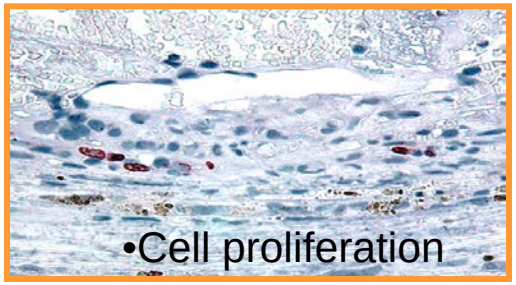
Cascade of Events Following Stent Placement In Animal Arteries

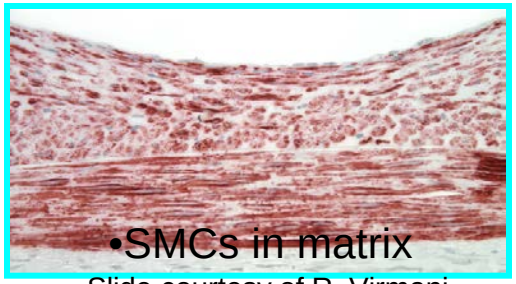


- Platelet Deposition
- Leukocyte recruitment
- VSMC proliferation /migration
- Matrix deposition







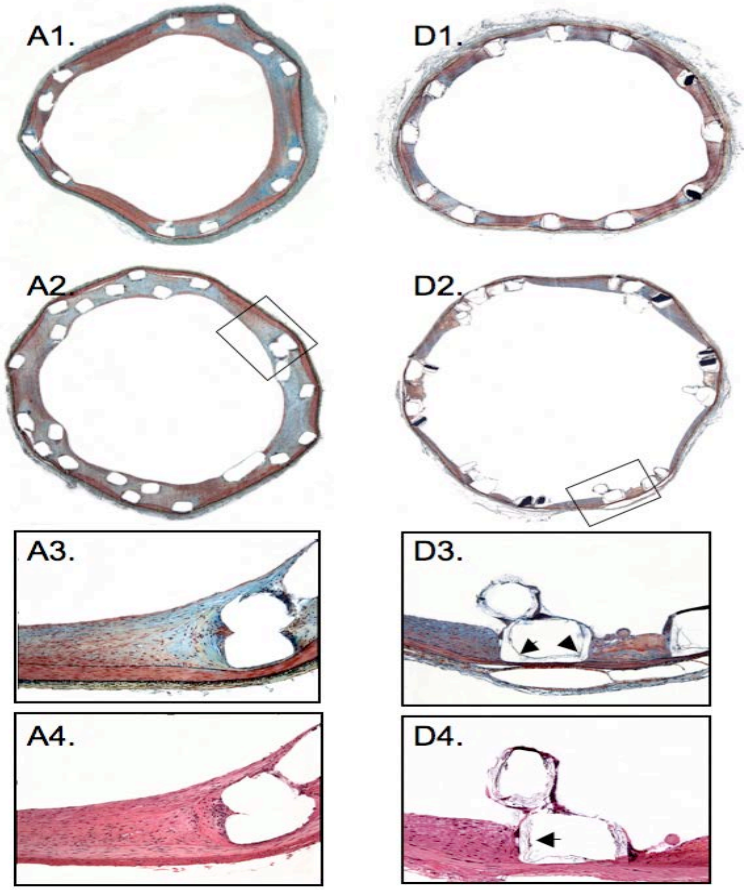


Slide courtesy of R. Virmani

Safety Endpoints

MORPHOMETRIC ANALYSIS and HISTOLOGIC GRADING SYSTEMS FOR:

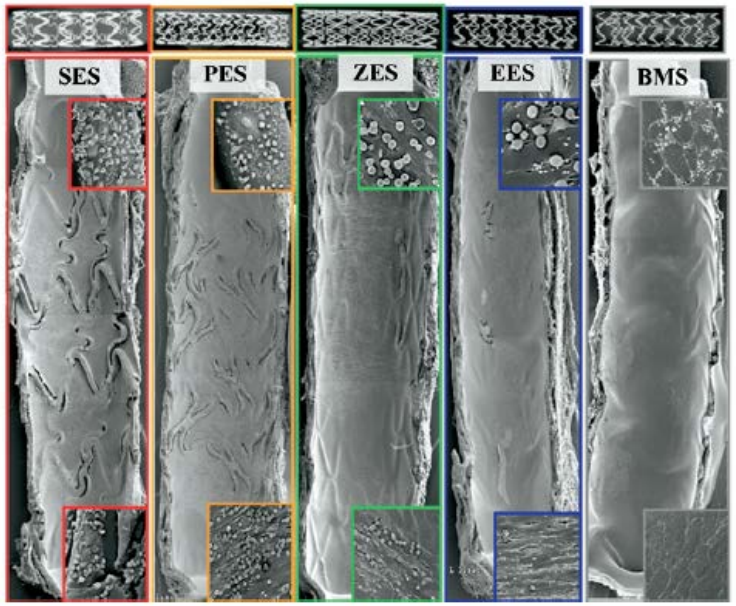
- Inflammation
  - WBC and Giant Cells
  - Granulomas
- Injury
  - Damage to IEL, EEL, Media and Adventitia
- Neointimal Response
  - Percent Stenosis
  - Neointimal area & thickness
  - Medial area & thickness
- Endothelialization
- Other
  - Hemorrhage
  - Thrombosis
  - Aneurysms
  - Fibrin Deposition
  - Calcification



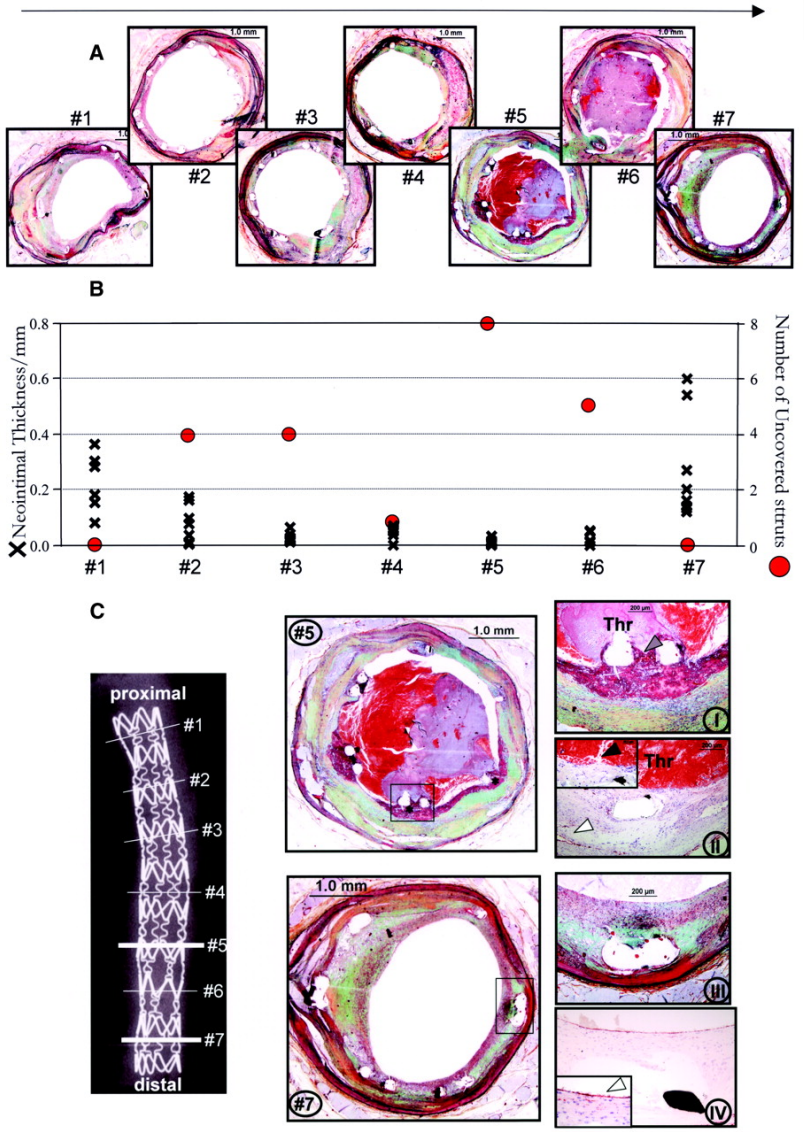
John et al. *JACC Interv*. 2008;1:535-44

Scanning Electron Microscopy

- Provides en face visualization of the stented vessel
- Can identify exposed (de-endothelialized) areas of the stent surface, which are potentially pro-thrombogenic



Joner et al. *JACC*. 2008;52:333-42



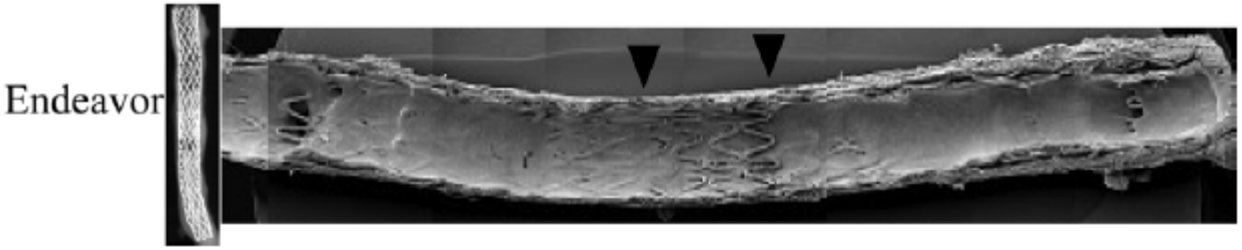
Finn A V et al. *Circulation*. 2007;115:2435-2441

Thrombogenicity Endpoints in Large Animal Studies

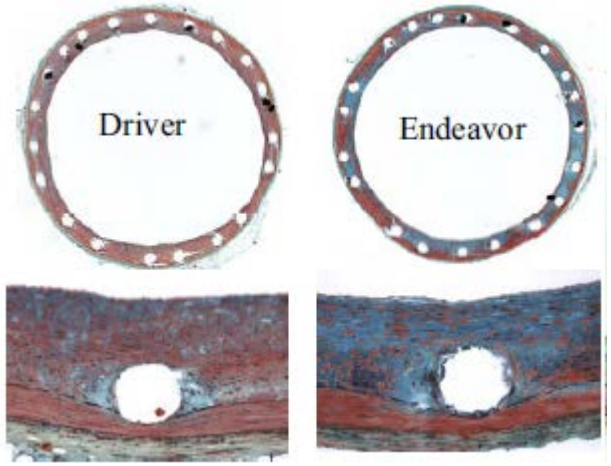
- Performance and handling evaluation
  - Gross evaluation of catheters
- 3-day acute study
  - Typically only applies to DES (coupled with acute tox testing)
  - Dynamic period of healing, challenging to interpret outcomes unless severe
- Mid to Long-term histology
- Clinical pathology

Case Study - Large Animal Data

SEM



28 Day Histology

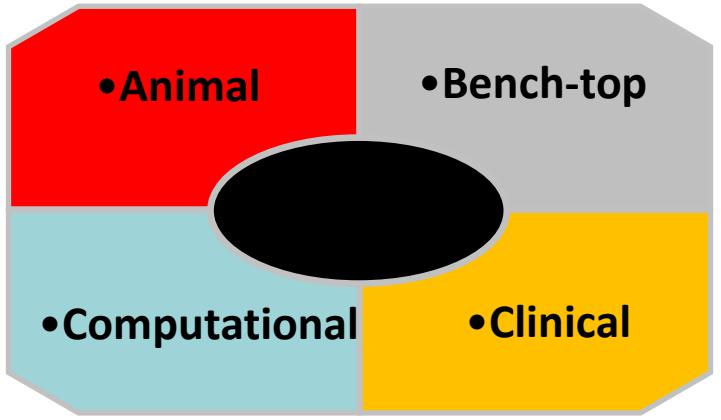


- Swine SEM and histology data show typical healing responses
- The canine and large animal data therefore demonstrate conflicting results
- How do we interpret the thrombogenic potential of this device?

Nakazawa et al. *AJC.* 2007;100:36M-44M

Device Evaluation: The Big Picture

- Device evaluation is a multi-factorial process
- Animal testing data is one component of a comprehensive evaluation of the device
- FDA reviews the totality of the data when evaluating the safety and effective-ness of a device



Pros and Cons

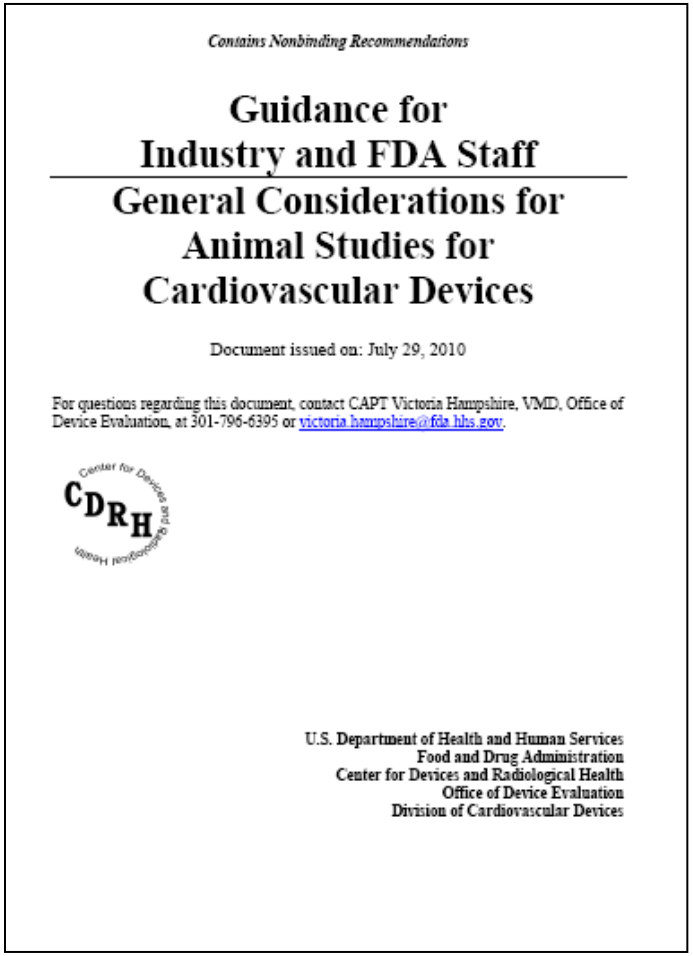
- Canine model
  - Pros
    - Small (n=2/3), short (acute) & relatively inexpensive
    - Suitable for iterative changes to device materials/geometry
  - Cons
    - Non-heparinized
    - Long catheter dwell time
    - Mismatch of catheter sizing to treatment vessel
    - Non-orthotopic placement
- Large Animal models (sheep and pig)
  - Pros
    - Clinically similar if not identical device placement
    - Multifaceted assessment of all biological responses (incl. thrombogenicity)
  - Cons
    - Cost and time-intensive

Concluding Remarks

- The utility of the canine model remains a complex issue
- More clinically relevant and/or reliable methods of thromboresistance evaluation are needed
- The large animal testing should be leveraged whenever possible
- Optimized canine or other testing may be indicated when new implant materials are being proposed, or if making a claim about materials being more hemocompatible
- Sponsors are encouraged to utilize the pre-submission process to ensure that the thrombogenicity testing strategy is appropriate

Animal Studies Guidance

- Guidance for Industry and FDA Staff: General Considerations for Animal Studies for Cardiovascular Devices – http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm220760.htm



Contains Nonbinding Recommendations

Guidance for Industry and FDA Staff

General Considerations for Animal Studies for Cardiovascular Devices

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For questions regarding this document, contact CAPT Victoria Hampshire, VMD, Office of Device Evaluation, at 301-796-6395 or victoria.hampshire@fda.hhs.gov.

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Thank You

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